REVIEW

Management of the Distal Ureter During Nephroureterectomy for Upper Tract Urothelial Carcinoma: A Comprehensive Review of Literature

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Purpose: Radical open nephroureterectomy (ONU) with bladder cuff excision (BCE) is the traditional gold standard approach for management of high-risk non-metastatic upper tract urothelial cancer. ONU involves two separate procedures; the nephrectomy and distal ureterectomy, with each of these parts being able to be performed with an open or minimally-invasive approach. Multiple approaches have been described for the resection of the distal ureter and bladder cuff after mobilization of the kidney and upper ureter.

Materials and Methods: A Medline search of the literature including relevant articles up to March, 2020 was performed. Search terms included "nephroureterectomy", "upper tract urothelial carcinoma", "upper urinary tract carcinoma OR UTUC", "open OR conventional OR ONU OR conventional", "robotic-assisted nephroureterectomy OR RANU", "laparoscop* OR LNU OR LRNU" and "minimally-invasive nephroureterectomy". Original articles, case series and review articles were included.

Results: There are no randomised studies. Various techniques have been described to manage the distal ureter during nephroureterectomy. This review provides an overview of these techniques. The perioperative and oncological outcomes following open versus endoscopic techniques and minimally invasive techniques have been described. Although endoscopic approaches have more favourable perioperative outcomes, this comes at the expense of increased risk of tumour spillage and recurrence compared to the traditional open approaches. Minimally-invasive techniques (laparoscopic and robotic-assisted NU) largely have superior perioperative outcomes versus their open NU counterparts, with comparable oncological outcomes.

Conclusion: Current non-randomised evidence is open to selection bias and is insufficient to support or refute endoscopic management of the distal ureter as an alternative to open bladder cuff excision. The optimal approach to nephroureterectomy and management of the distal ureter continues to remain a surgical dilemma.

Keywords: nephroureterectomy; ureteral neoplasms; carcinoma, transitional cell

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is rare, comprising 5-10% of all urothelial cancers(1). It can involve the urothelial lining anywhere from the renal calyces down to the distal ureteric orifice. Radical open nephroureterectomy (ONU) with bladder cuff excision (BCE) is the traditional gold standard approach for management of high-risk non-metastatic UTUC, recommended by the European Association of Urology guidelines(2). High-risk UTUC is defined as having any of the following factors present: hydronephrosis, tumour size greater than 2 cm, high-grade cytology, high-grade URS biopsy, multifocal disease, previous radical cystectomy for high-grade bladder cancer, or variant histology(2). Due to the propensity for recurrence seen with this type of malignancy, the surgical approach involves complete en bloc resection of the kidney, ipsilateral ureter, and bladder cuff, regardless of the location of the lesion along the urinary tract. It is imperative this be done in a manner that is oncologically-sound, whereby tumour spillage and seeding are avoided(3,4).

Previously, surveillance following NU has remained as the standard of care for UTUC, with systemic chemotherapy not being recommended(5). However, recent level 1 RCT evidence from the POUT trial(6) assessed the efficacy of adjuvant platinum-based chemotherapy in patients with locally-advanced UTUC, showing that gemcitabine-platinum combination chemotherapy administered within 90 days after NU reduces rates of recurrence and improves disease-free survival. This study suggests that adjuvant chemotherapy be recommended as the new guideline for management post-NU.

ONU involves two separate procedures; the nephrectomy and distal ureterectomy, with each of these parts being able to be performed with an open or minimally-invasive approach. Multiple approaches have been described for the resection of the distal ureter and bladder cuff after mobilization of the kidney and upper ureter. It has been shown that if the distal intramural ureter

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Table 1a. Contemporary (2009 – 2021) oncological data comparing endoscopic vs non-endoscopic approaches

Study and year	**Approach to NU and distal ureter**	**Patients (N)**	**Mean age (years)**	**Length of follow-up (months)**	**Intravesical recurrence no. (%)**	**Other recurrence no. (%)**	**CFS, OS, CSS (%) Metastasis no. (%)**	**DSM (disease-specific mortality), n (%)**
Xylinas et al. 2014 (36)	Transvesical Extravesical Endoscopic	1811 785 85	68.7 67.7 69.6	61.1 52.3 36.1	388 (21.4) 160 (20.3) 29 (34.1)	526 (29) 204 (25.9) 18 (21.2)	RFS: 66 CSS: 71 OS: 66 RFS: 66 CSS: 70 OS: 66 RFS: 69 CSS: 82 OS: 69	419 (23.1) 175 (22.3) 11 (12.9)
Chiang et al. 2011 (37)	Hand-assisted retroperitoneoscopic Transurethral bladder cuff incision-assisted	98 110	67.54 65.2	25.28 27.88	26 (26.53) 32 (29.09)	12 (12.24) 11 (10.00)	Mets: 14 (14.29) Mets: 11 (10.00)	6 (6.12) 9 (8.18)
Fragkoulis et al. 2017 (38)	Open Transurethral	192 186	69.2 68.7	60	46 (24) 50 (27)	-	CSS: 74 CSS: 75	-
Kapoor et al. 2014 (7)	Extravesical Intravesical Endoscopic	316 406 98	69.9 69.2 70.0	24.6 -	77 (24.4) 66 (16.3) 23 (23.5)	-	RFS: 35.6 RFS: 46.3 RFS: 30.1	136 (16.6)
Kim et al. 2014 (39)	Hand-assisted retroperitoneoscopic	28	68	-	6 (21.4)	-	-	-
Li et al. 2010 (40)	Intravesical Extravesical Transurethral	81 129 91	65.4	33 39 30	19 (23.5) 31 (24.0) 16 (17.6)	10 (12.3) 15 (11.6) 7 (7.7)	Mets: 6 (7.4) Mets: 13 (10.1) Mets: 5 (5.5)	15 (18.5) 17 (13.2) 9 (9.9)
Ou and Yang 2014 (41)	Hand-assisted retroperitoneoscopic: no ureteral ligation Hand-assisted retroperitoneoscopic: earlier ureteral ligation	30 31	69.9 67.8	25.8 53.1	7 (23) 11 (35)	1 4	Mets: 0 Mets: 2	-
Cormio et al. 2013 (42)	Open with transurethral distal ureter balloon occlusion and detachment	13	64.7	39.8	4 (30.1)	0 (1)	-	-
Cormio et al. 2014 (43)	Open with flexible cystoscope-assisted transurethral distal ureter balloon occlusion and detachment	10	68.2	31.1	2 (20.0)	0 (0)	-	-
Geavlete et al. 2012 (44)	Endoscopic pluck with bipolar plasma vaporisation	42	-	14	6 (14)	2 (5)	-	2 (4.8)
Gillan et al. (45)	Laparoscopic Endoscopic Open	6 12 12	73.6 75.2 71.8	12	0 (0) 2 1	-	-	-
Lai et al. (46)	Intravesical Extravesical Transurethral endoscopic	99 96 53	69	44.2	(17.2) (12.5) (13.2)	-	CSS: (11.1) CSS: (5.2) CSS: (7.5)	20 (8.1)
Ryoo et al. (47)	Transvesical resection Extravesical ligation	477 379	64.4 65.3	36.5 38.2	157 (32.9) 163 (43.0)	-	Intravesical recurrence-free survival IVRFS: 59.9 CSS: 82.0 OS: 79.7 IVRFS: 49.3 CSS: 73.8 OS: 68.0	-
Allard et al. (48)	Extravesical Intravesical Transurethral incision	29 20 61	72.4 70.4 70.1	22	8 (26.7) 7 (35.0) 19 (31.1)	Urothelial recurrence : 8 (26.7) Urothelial recurrence: 8 (38.1) Urothelial recurrence: 20 (32.8)	Mets: 6 (20.6) Mets: 2 (10.0) Mets: 10 (16.4)	-
Carrion et al. (49)	Endoscopic resection Endoscopic bladder cuff Open extravesical Open intravesical	32 57 21 42	70 70.1 67.8 70.81	32	5 (15.6) 9 (15.8) 4 (19) 20 (47.6)	7 (21.9) 13 (22.8) 11 (52.4) 11 (26.2)	CSS: 84 months CSS: 89 months CSS: 48 months CSS: 71 months	5 (15.6) 10 (17.5) 11 (52.4) 10 (23.8)
Bragayrac et al. (50)	Transvesical laparoendoscopic single-site	5	70	16.2	0 (0)	-	Mets: 1 (20)	-
Pang et al. (51)	Open Transurethral electrosurgery Transurethral endoscopic two-micron thulium laser resection	24 17 17	-	-	5 4 2	1 0 0	-	-

Table 1b. Contemporary (2009 – 2021) oncological data comparing ONU vs minimally-invasive NU

Study and year	**Approach to NU and distal ureter**	**Patients (N)**	**Mean age (years)**	**Length of follow-up (months)**	**Intravesical**	**Other recurrence no. (%)**	**CFS, OS, CSS (%) Metastasis no. (%)**	**DSM (disease-specific mortality), n (%)**
Ariane et al. (52)	Open Laparoscopic	459 150	69.8 69.5	40.4 24.5	-	-	CSS: 78.0 RFS: 50.7 Mets: 97 (21.1) CSS: 90.7 RFS: 52.2 Mets: 21 (14)	-
Blackmur et al. (53)	Open Laparoscopic	13 13	67.5 68.0	57.0 25.8	4 (30.8) 4 (30.8)	1 (7.7) 4 (30.8)	OS: 73.5 PFS: 56.0 CSS: 73.5 OS: 59.1 PFS: 24.0 CSS: 60.9	-
Eandi JA et al. (54)	Robotic-assisted	11	67.4	15.2	4 (36.4)	-	-	Mets: 2 (18.2) 4 (36.4)
Fairey et al. (55)	Open Laparoscopic	403 446	70.5 72.4	26	-	-	OS: 67 DSS: 73 RFS: 43 OS: 68 DSS: 76 RFS: 33	-
Favaretto RL et al. (56)	Open Laparoscopic	109 53	71 73	23	51 (31.5) 15 (9.3)	19 (11.7) 14 (8.6)	CSS: 86 RFS: 38 CSS: 82 RFS: 42	26 (16.0) 9 (5.6)
Hemal et al. (34)	Robotic-assisted	15	66.27	Short-term	0	0	-	-
Lim et al. (57)	Robotic-assisted	32	66.5	45.5	10 (31.3)	14 (43.8)	OS: 60.9 CSS: 75.8 RFS: 68.1	7 (21.9)
Park et al. (58)	Laparoscopic	101	66.4	14	Distant + bladder recurrence: 22.8	Distant + bladder recurrence: 22.8	-	6 (5.9)
Walton et al. (59)	Open Laparoscopic	703 70	68 70	36 17	-	165 (23.5) 17 (24.3)	RFS: 73.7 CSS: 75.4 RFS: 63.4 CSS: 75.2	146 (20.8) 9 (12.9)
Capitano et al. (60)	Open Laparoscopic	979 270	68.3 70.2	62	-	Total recurrence: 250 (25.5) Total recurrence: 27 (10.0)		CSS: 73.1 RFS: 76.2 CSS: 85.8 RFS: 86.8 217 (22.8) 21 (7.8)
Wang et al. (61)	Open Laparoscopic	72 86	66.1 68.7	42.4	18 (25.0) 16 (18.6)	7 (9.7) 15 (17.4)	CSS: 80.3 RFS: 59.2 CSS: 80.7 RFS: 62.8	12 (16.7) 10 (11.6)
Zou et al. (62)	Open Laparoscopic	101 21	63.8 63.2	53	-	-	CSS: 79.2 CSS: 85.7	-
Simone et al. (63)	Open Laparoscopic	40 40	61.3 59.6	44	9 (22.5) 10 (25.0)	-	CSS: 89.9 Mets: 6 (15) MFS (metastasis-free survival): 77.4 CSS: 79.8 Mets: 11 (27.5) MFS: 75.5	4 (10) 8 (20)
Greco et al. (64)	Open Laparoscopic	70 70	67.2 66.4	60	5 (7.1) 3 (4.3)	-	DFS (disease-free survival):73 DFS: 75	-
Kamihira et al. (65)	Laparoscopic	1003	68.6	20	(43)	134 (13.4)	RFS: 42 OS: 70	(4)
Kitamura et al. (66)	Open Hand-assisted laparoscopic Laparoscopic	34 9 65	69 65 **70**	70	-	-	CSS: 74.2 RFS: 57.1 CSS: 72.9 RFS: 12.5 CSS: 87.4 RFS: 69.2	-
Lim et al. (67)	Robotic-assisted	38	66.5	40.6	10 (26.3)	145 (39.5)	-	7 (18.4)
Pugh et al. (68)	Robotic-assisted	43	68.3	9.6	6 (14)	3 (7)	-	-
Yang et al. (69)	Robotic-assisted	20	70.1	14.7	3 (15)	4 (20)	Mets: 4 (20)	-
Miyazaki et al. (70)	Open Laparoscopic	527 222	69.5 70.1	39.0	174 (33.0) 69 (31.1)	64 (12.1) 27 (12.2)	OS: 69.5 CSS: 73.0 Mets: 186 (35.3) OS: 72.4 CSS: 76.0 Mets: 75 (33.8)	- -
Stewart et al. (71)	Open Laparoscopic	39 23	68.1 67.4	177 146	15 (39) 9 (39)	-	OS: 64 PFS (progression -free survival): 79 CSS: 80 OS: 61 PRS: 76 CSS: 71	8 (21) 7 (30)
Aboumohamed et al. (31)	Robotic-assisted	65	69.1	25.1	15 (27.2)	13 (20)	OS: 62.6 CSS: 92.9 RFS: 57.1 Mets: 8 (13.3)	-
Ambani et al. (72)	Robotic-assisted Laparoscopic	22 22	70.1 70.8	10 15	8 (36) 7 (37)	7 (32) 5 (23)	-	2 (9) 2 (9)
Badani et al. (33)	Robotic-assisted	26	66	7.8	4 (15)	0 (0)	-	-
Chen et al. (73)	Open with early ligation of distal ureter Open with late ligation of distal ureter	42 43	63 67	28	21 (25)	5(6)	-	-
Hattori et al. (26)	Laparoscopic	10	19	19	1 (10)	3 (30)	-	1 (10)
Hu et al. (74)	Robotic-assisted Hand-assisted laparoscopic	18 197	70.4 67.7	6.1 47.8	2 (11.1) 6 (33.3)	0 (0) 2 (11.1)	Mets: 4 (22.2) Mets: 2 (11.1)	1 (5.6) 3 (16.7)

Study and year	Approach to NU and distal ureter	Patients (N)	Mean age (years)	Length of follow-up (months)	Intravesical	Other recurrence no. (%)	CFS, OS, CSS (%) Metastasis no. (%)	DSM (disease-specific mortality), n (%)
Lambert et al. (75)	Laparoscopic	22	65.6	20	3 (13.6)	2 (9.1)	-	-
Liu et al. (76)	Laparoscopic	31	66.8	10.5	0 (0)	0 (0)	-	-
Mak et al. (77)	Pneumovesicum-assisted laparoscopic	10	71.6	46	4 (40)	1 (10)	-	-
Ritch et al. (27)	Open Laparoscopic stapling Laparoscopic resection and suturing	10 14 12	68 70 71	16 21 7	2 (20) 2 (14.3) 0 (0)	0 (0) 2 (14.3) 0 (0)	Mets: 0 (0) Mets: 2 (14.3) Mets: 0 (0)	0 (0) 1 ((7.1) 0 (0)
Shoma et al. (78)	Laparoscopic	13	50	31.5	2 (15)	1 (8)	-	1 (8)
Song et al. (79)	Hand-assisted laparoscopic	67	66.2	17.6	9 (13)	9 (13)	Mets: 9 (13)	2 (3)
Waldert et al. (80)	Open Laparoscopic	59 43	68.46 65.56	41 41	16 (27) 11 (26)	13 (22) 5 (12)	CFS: 76 CSS: 80 Mets: 7 (12) CFS: 79 CSS: 85 Mets: 5 (11)	-
Ziaee et al. (81)	Laparoscopic NU with open BCE	22	64.1	36.57	3 (4)	2 (9)	3-yr OS: 95 3-yr metastasis-free survival: 90	1 (4.5)
Gillan et al. (45)	Laparoscopic Endoscopic Open	6 12 12	73.6 75.2 71.8	12	0 (0) 2 1	-	-	-
Hora et al. (82)	Laparoscopic	12	71.3	25.7	1 (8.3)	-	Mets: 1 (8.3)	-
Pai et al. (83)	Laparoscopic	59	67	58	9 (53)	8 (47)	CSS: 80	-
Agarwal et al. (18)	Laparoscopic with Poly Loop ligation	6	64.2	12-30	2 (33.3)	0 (0)	-	-
Hoe et al. (19)	Laparoscopic with PolyLoop Ligation	76 71.5	Bladder RFS: 24.3 Contralateral RFS 47.9: Local RFS: 49.8 MFS (metastasis-free survival): 52.5 OS: 52.5 CSS: 47.9		0 (0)	-	OS: 70.3 CSS: 84.7 Bladder RFS: 59.6 Local RFS: 89.0 Contralateral RFS: 93.5 Metastasis-free survival: 73.5 Port-site metastasis: 0 (0)	-
Carrion et al. (84)	Laparoscopic	117 70	20		5 (14)	36 (30)	CSS: 61 Progression-free survival: 52	28 (24)
Krabbe et al. (11)	Laparoscopic with no transvesical bladder cuff Laparoscopic with transvesical bladder cuff	46 69.5 76 68.0	32.0		12 (26.1) 33 (43.4)	13 (28.3) 10 (13.2)	Intravesical recurrence-free survival (IVR FS): 71.6 months Non-IVR FS: 120.0 CSS: 123.5 months IVR-FS: 82.5 months Non-IVR FS: 83.9 months CSS: 83.0 months	22 (18.0)
Shigeta et al. (85)	Laparoscopic	129 71	31.1		61 (47.3)	-	CSS: 29.5 months OS: 35.6 months	31 (24.0)
Guo et al. (86)	Laparoscopic with 2-micrometer continuous wave laser	38 65.3	36.5		4 (10.5)	0 (0)	CSS: 100 Bladder recurrence-free rate: 89 Extravesical recurrence-free rate: 100 Mets: 0 (0)	-
Zou et al. (87)	Laparoscopic one-port pneumovesicum	6 57.2	18		0 (0)	0 (0)	-	-
Liu et al. (88)	Open Laparoscopic	213 62.5 52 60.2	44		40 (18.8) 6 (11.5)	Total recurrence: 109 (51.1) Total recurrence: 20 (38.5)	Intravesical RFS: 79 Overall RFS: 47 Mets: 71 (33.3) CSS: 63 OS: 61 Intravesical RFS: 88 Overall RFS: 59 Mets: 13 (25.0) CSS: 70 OS: 55	-
Bragayrac et al. (50)	Transvesical laparoendoscopic single-site	5 70	16.2		0 (0)	-	Mets: 1 (20)	-
Lee et al. (89)	Robotic-assisted	20 71	13.5		-	1	-	-
Khanna et al. (90)	Robotic-assisted	3 69.3	17.8		0 (0)	0 (0)	-	-
Ghazi et al. (17)	Laparoscopic	8 65.3	12.1		3 (37.5)	1 (12.5)	-	-
Vasdev et al. (91)	Robotic-assisted Lister technique	7 -	59		0 (0)	-	-	-

Table 2a. Contemporary (2009 – 2021) perioperative outcomes comparing endoscopic vs non-endoscopic approaches

Study and year	Approach to NU	Patients (N)	Mean age (years)	Complication rate, no. (%)	Clavien Classification ≥ 3 (III-V)	Mean operating time (min)	Mean length of hospital stay (days), range	Estimated blood loss (mL)
Chen et al. (73)	Open with early ligation of distal ureter	42	63	-	0 (0)	220.19	9.5	105.15
	Open with late ligation of distal ureter	43	67		0 (0)	215.73	10	110.12
Chiang et al. (37)	Hand-assisted retroperitoneoscopic	98	67.54	-	-	144	7.3	67
	Transurethral bladder cuff incision-assisted	110	65.2			173	8.8	86
Fragkoulis et al. (38)	Open	192	69.2	-	-	143	7.1	-
	Transurethral resection/Pluck	186	68.7			115	6.9	
Cormio et al. (42)	Open with transurethral distal ureter balloon occlusion before detachment	13	64.7	1 (7.7)	0 (0)	Open NU: 108 Distal ureter and BCE: 21.3	8.1 (5-10)	-
Cormio et al. (43)	Open with flexible cystoscope-assisted transurethral distal ureter balloon occlusion and detachment	10	68.2	0 (0)	-	113.4	6.5 (5-10)	-
Geavlete et al. (44)	Endoscopic pluck with bipolar plasma vaporisation	42	-	2 (4.8)	-	15	-	-
Gillan et al. (45)	Laparoscopic	6	73.6	0 (0)	-	190	6.3 (4-8)	200
	Endoscopic	12	75.2	0 (0)		180	7.1 (5-12)	180
	Open	12	71.8	1		200	12 (7-19)	240
Pang et al. (51)	Open	24	-	-	-	233	12.7	352.0
	Transurethral electrosurgery	17				148.1	9.8	136.5
	Transurethral endoscopic two-micron thulium laser resection	17				126.5	9.9	141.0

is not fully excised and a ureteric stump left behind, the risk of recurrence is anywhere from 33-75%[7]. Lughezzani et al. reported a 1.25-1.45 times increased risk of cancer-specific mortality if the bladder cuff excision was omitted[8].

Here we will review the various surgical techniques and current literature on the management of the distal ureter during nephroureterectomy.

MATERIALS AND METHODS

A Medline search of the literature including relevant articles up to March, 2020 was performed. Search terms included "nephroureterectomy", "upper tract urothelial carcinoma", "upper urinary tract carcinoma OR UTUC", "open OR conventional OR ONU OR conventional", "robotic-assisted nephroureterectomy OR RANU", "laparoscop* OR LNU OR LRNU" and "minimally-invasive nephroureterectomy". Original articles, case series and review articles were included.

RESULTS

Approaches to the distal ureter

Various approaches have been described as seen in Figure 1. The standard practice is to remove the intramural ureter along with ureteric orifice (UO), and a cuff of bladder around the UO. Ideally, this is achieved by an en bloc removal of specimen after controlled occlusion of the UO. In a systemic review and meta-analysis of clinicopathologic factors associated with intravesical recurrence after RNU by Seisen et al[9] it was shown that there is significant risk of tumor recurrence in the distal ureter and its orifice. Poorer cancer-specific survival and overall survival has been seen in patients who did not have a bladder cuff excision during their NU[10,11].

The optimal approach to managing the distal ureter and bladder cuff has been controversial due to different techniques described. These techniques can be classified as open (intravesical/transvesical approaches), endoscopic or minimally-invasive approaches, with some techniques employing a combination of these[12]. The open approach has been traditionally regarded as the gold standard[2]. However, advances in minimally-invasive technology have enabled urologists to expand their armamentarium in managing the distal ureter. The challenges of all these techniques are to remove the entire specimen en bloc, without tumour spillage, and to conform to strict oncological principles in the least invasive way possible.

Open excision (ONU)

An open approach to the distal ureter is considered the gold standard for excision of the distal ureter and bladder cuff. It is generally performed after the nephrectomy is complete, occurring after either a laparoscopic or open procedure to dissect the kidney and ureter. The distal ureter may then be approached in two ways, either intravesically/transvesically or extravesically[13].

The intravesical or transvesical approach begins with an anterior cystotomy to provide access to the bladder cuff, followed by dissection of the ureter. Once the contralateral ureteral orifice is identified, followed by a 5-10 mm circumferential excision around the ipsilateral ureteral orifice through the full thickness of the bladder. The intramural ureter is dissected until the proximal ureteral dissection is reached, allowing the specimen to be removed en bloc. Benefits to this technique include better visualisation of the contralateral ureter and intramural

Table 2b. Contemporary (2009 – 2021) perioperative outcomes comparing ONU vs minimally-invasive NU

Study and year	Approach to NU	Patients (N)	Mean age (years)	Complication rate, no. (%)	Clavien Classification ≥ 3 (III-V)	Mean operating time (min)	Mean length of hospital stay (days), range	Estimated blood loss (mL)
Ariane et al. (52)	Open	459	69.8	23 (5)	19 (4.1)	180	9 (7-12)	-
	Laparoscopic	150	69.5	9 (6)	7 (4.6)	240	8 (6-12)	
Blackmur et al. (53)	Open	13	67.5	4 (30.8)	2 (15.4)	194	10 (5-29)	-
	Laparoscopic	13	68.0	3 (23.1)	0 (0)	191	7 (3-10)	
Eandi JA et al. (54)	RALNU	11	67.4	-	-	326	4.7	200
Favaretto RL et al. (56)	Open	109	71	-	-	164	5 (4-6)	250
	Laparoscopic	53	73			265	3 (3-4)	200
Hemal et al. (34)	Robotic -assisted	15	66.27	0 (0)	-	183.87	2.73 (2-5)	103
Lim et al. (57)	Robotic-assisted	32	66.5	7 (28.1)	2 (6.2)	250.1	6.2	263
Park et al. (58)	Laparoscopic	101	66.4	6 (5.9)	1 (1.0)	221.4	6.3	231.7
Wang et al. (61)	Open	72	66.1	-	-	148.5	7.3	286.1
	Laparoscopic	86	68.7			133.2	5.5	176.3
Simone et al. (63)	Open	40	61.3	0 (0)	-	78	3.65 (3-5)	430
	Laparoscopic	40	59.6			82	2.3 (2-3)	104
Greco et al. (64)	Open	70	67.2	-	240	-	-	190
	Laparoscopic	70	66.4	-				
Kamihira et al. (65)	Laparoscopic	1003	68.6	93 (9.3)	-	320	-	232
Kitamura et al. (66)	Open	34	69	5 (15)	-	286	14.5 (5-36)	475
	Hand-assisted laparoscopic	9	65	2 (22)		325	17 (9-24)	250
	Laparoscopic	65	70	7 (11)		327	10 (4-62)	220
Lee et al. (92)	Laparoscopic	10	62.79	4 (40)	-	225.63	4.75	187.50
Lim et al. (67)	Robotic-assisted	38	66.5	10 (25.0)	2 (5.3)	249	6.0	264
Pugh et al. (68)	Robotic-assisted	43	68.3	6 (14)	-	247	3 (2-87)	131
Trudeau et al. (93)	Laparoscopic	735	70.6	134 (18.2)	-	-	5.83	-
	Robotic-assisted	715	70.7	85 (11.9)			5.6	
Yang et al. (69)	Robotic-assisted	20	70.1	0 (0)	-	251.6	6.7 (4-12)	50.0
Hanske et al. (94)	Minimally-invasive (laparoscopic + robotic-assisted)	599	71	77 (12.9)	-	160 (26.7) > 282 mins	137 (22.9) > 6 days	-
	Open	297	69	37 (12.5)		66 (22.2) > 282 mins	135 (45.5) > 6 days	-
Stewart et al. (71)	Open	39	68.1	-	5 (12.8)	180	10 (5-29)	398
	Laparoscopic	23	67.4		1 (4.3)	165	7 (2-30)	280
Ambani et al. (72)	Robotic-assisted	22	70.1	8 (36.4)	1 (5)	298	3.1	380
	Laparoscopic	22	70.8	6 (27.3)	1 (5)	251	3.1	233
Badani et al. (33)	Robotic-assisted	26	66	0 (0)	-	230	2 (1-15)	66
Chen et al. (73)	Open with early ligation of distal ureter	42	63	-	0 (0)	220.19	9.5	105.15
	Open with late ligation of distal ureter	43	67		0 (0)	215.73	10	110.12
Hu et al. (74)	Robotic-assisted	18	70.4	-	-	255.17	6.79 (3.7-12)	68.89
	Hand-assisted laparoscopic	197	67.7			250.17	9.61 (4-26)	358.33
Kim et al. (39)	Hand-assisted retroperitoneoscopic	28	68	5 (17.9)	-	240	8 (5-10)	250
Lambert et al. (75)	Laparoscopic	22	65.6	4	-	227	3.5 (1-13)	158
Liu et al. (76)	Laparoscopic	31	66.8	0 (0)	-	146.6	6 (4-8)	47.3
Mak et al. (77)	Laparoscopic	10	71.6	1 (10)	-	7.5	10.2 (6-16)	Minimal
Ritch et al. (27)	Open	10	68	1 (10)	-	276	3.5 (2-6)	163
	Laparoscopic stapling	14	70	1 (7)		152	2.7 (2-7)	209
	Laparoscopic resection and suturing	12	71	1 (8)		163	2.0 (1-3)	112
Shoma et al. (78)	Laparoscopic	13	50	3 (23.1)	-	226	7	233
Song et al. (79)	Hand-assisted laparoscopic	67	66.2	1	-	243.5	8.1	-
Waldert et al. (80)	Open	59	68.46	2 (3)	-	212	13.8 (9-16)	542
	Laparoscopic	43	65.56	1 (2)		220	8.1 (7-9)	300

Study and year	Approach to NU	Patients (N)	Mean age (years)	Complication rate, no. (%)	Clavien Classification ≥ 3 (III-V)	Mean operating time (min)	Mean length of hospital stay (days), range	Estimated blood loss (mL)
Ziaee et al. (81)	Laparoscopic NU with open BCE	22	64.1	2 (9)	-	216	4.3	314
Gillan et al. (45)	Laparoscopic	6	73.6	0 (0)	-	190	6.3 (4-8)	200
	Endoscopic	12	75.2	0 (0)		180	7.1 (5-12)	180
	Open	12	71.8	1		200	12 (7-19)	240
Hora et al. (82)	Laparoscopic	12	71.3	1 (8.3)	-	164.9	9.3	150.0
Pai et al. (83)	Laparoscopic	59	67	2 (3)	2 (3)	194.4	3.4	125
Agarwal et al. (18)	Laparoscopic with PolyLoop ligation	6	64.2	0 (0)	-	27	-	Minimal
Hoe et al. (19)	Laparoscopic with PolyLoop Ligation	76	71.5	23 (30.3)	3 (3.9)	258	6 (3-23)	-
Guo et al. (86)	Laparoscopic with 2-micrometer continuous wave laser	38	65.3	1 (2.6)	-	126	9.6 (5-20)	69.4
Zou et al. (87)	Laparoscopic one-port pneumovesicum	6	57.2	0 (0)	-	114	8.2 (8-9)	89
Bragayrac et al. (50)	Transvesical laparoendoscopic single-site	5	70	2 (40)	0 (0)	198	3.8 (2-8)	234
Roslan et al. (95)	Transvesical laparoendoscopic single-site	5	57.4	1 (20)	-	59	5.2 (4-9)	54
Vasdev et al. (91)	Robotic-assisted Lister technique	7	-	-	0 (0)	241.4	3 (3-7)	101.9
Lee et al. (89)	Robotic-assisted	20	71	2 (10)	0 (0)	161.3	3 (1-16)	98.8
Won Lee et al. (96)	Robotic-assisted	68	56	3 (4.4)	-	219	4.5 (1-16)	319
Khanna et al. (90)	Robotic-assisted	3	69.3	1	-	300	3.3	183
Ghazi et al. (17)	Laparoscopic	8	65.3	1 (12.5)	-	157	10.2 (7-15)	-

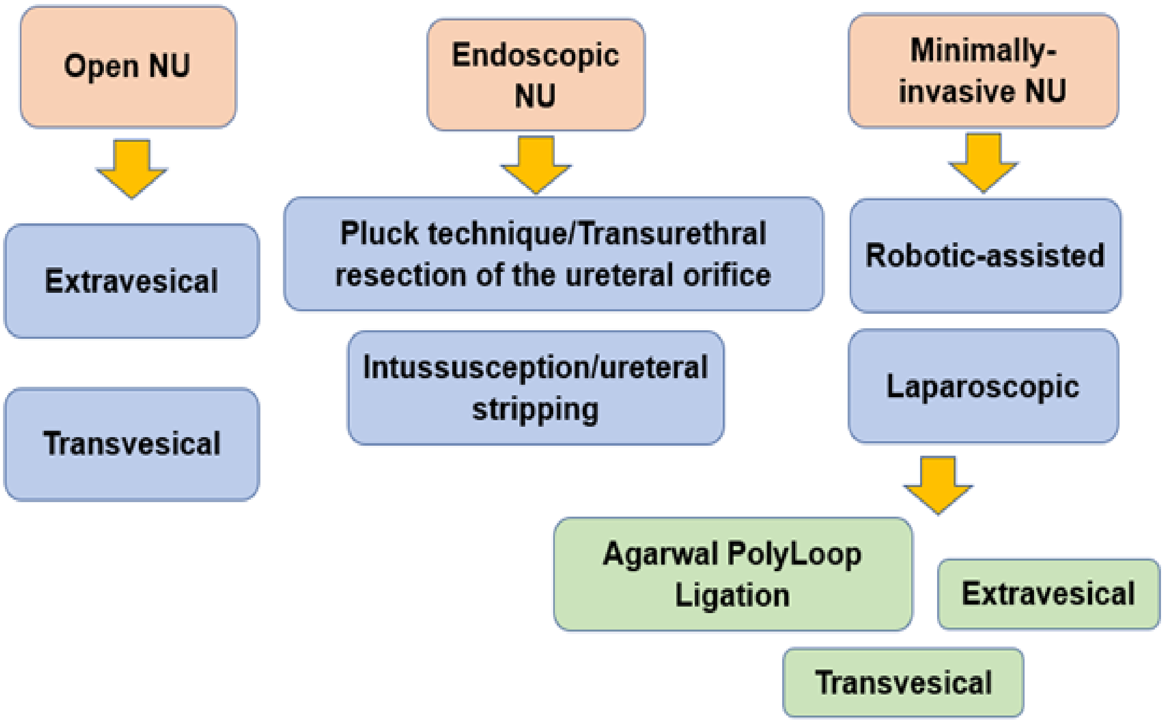

Figure 1. Overview of techniques used to manage the distal ureter during nephroureterectomy

ureter and enabling visual confirmation of excision of the bladder cuff. The anterior cystostomy is then closed in two layers. However, there is increased morbidity and longer patient recovery time due to an additional low abdominal incision and cystotomy. This technique should be avoided in patients with bladder urothelial carcinoma, as there is a risk of tumour seeding into the extravesical space[14].

The extravesical approach involves mobilisation of the distal ureter down to its insertion into the bladder, securing the bladder cuff with a right-angle clamp, and excising the intramural ureter along with its cuff in a similar 5-10 mm circumferential excision. The specimen is then removed en bloc. Compared to the transvesical approach, there is a shorter patient recovery time due to the lack of additional surgical incisions required [14]. However, there is the potential for damage to the contralateral ureter and incomplete excision of the distal ureter and bladder cuff due to poorer access and visualisation of the intramural ureter and bladder cuff[3].

Endoscopic excision

The distal ureter can also be approached endoscopically using the pluck technique, also referred to as transurethral resection/excision of the ureteral orifice, or intussusception, also known as the stripping technique.

The pluck technique begins prior to nephrectomy, where the ureteral orifice and bladder cuff is endoscopically circumscribed and resected with a Collins knife or resectoscope through the intramural portion of the ureter into the perivesical fat[15]. Following nephrectomy and after dissecting the ureter, the distal ureter is detached or 'plucked' from its attachment to the bladder, and removed along with the whole specimen[16]. An issue with this technique includes the potential for locoregional tumour recurrence following spillage of tumour cells from an unclamped ureter into the perivesical space. Other issues include fluid shifts due to usage of bladder irrigant and the potential for incomplete resection of the ureter if remnant ureter remains following plucking. The pluck technique is therefore contraindicated in patients with distal ureteral tumours[17]. To minimise the risk of tumour seeding, early coagulation of the ureteral orifice before dissecting the bladder cuff and early ligation of the ureter before nephroureterectomy recommended.

Agarwal et al.[18] and Hoe et al.[19] suggest a novel modification to this pluck technique called the Agarwal loop-ligation technique involving endoscopic loop ligation in a bid to occlude the ureter. Following dissection of the distal ureter and bladder cuff with the Collins knife, a PolyLoop placed around the ureteric stump to ligate and occlude the distal ureter, preventing urine spillage from the upper tract. Complete excision of distal ureter is ensured as the distal end is marked with the detachable loop. The distal ureteral stump is ligated prior to detaching the ureter or exposing the perivesical fat, providing protection against urine spillage into perivesical space. The distal ureter is then dissected by dividing the periureteric adhesions with a Collins knife. Although the outcomes of this technique were only analysed in a small series of 6 patients, no perioperative complications were present and with no perivesical tumour recurrence reported in the short-term.

The intussusception technique takes place following nephrectomy. The ureter is dissected as distally as possible. Then, a bulb-tipped ureteric catheter (Chevassu catheter) is inserted past the resected and open end of the ureter. It is then folded over on itself and sutured in place. After resecting the intramural ureter and ureteral orifice endoscopically, the catheter is pulled out, bringing the intussuscepted ureter with it, thus allowing for the entire distal ureter to be removed. The patient is transferred into a lithotomy position to allow for transurethral access and the catheter is pulled inward, causing intussusception of the distal ureter into the bladder. Excision is facilitated with a resectoscope[13]. Issues with this technique include inadequate removal of the distal ureter following stripping and the risk of tumour spillage into the perivesicle space, much like the pluck technique[17]. Contraindications to this technique are similar to the pluck technique, mainly urothelial carcinoma involving the distal ureter as there is a higher likelihood of incomplete resection with a positive margin. Additionally, patients with duplicated ureters, ureteral strictures, prior ureteral surgery, and prior radiation should undergo a different strategy to excise the bladder cuff and distal ureter[13].

Minimally-invasive excision

Laparoscopic and robotic-assisted techniques comprise the minimally-invasive methods of managing the distal ureter, and are regarded as the contemporary counterparts to ONU. In both, early ligation of the ureter during nephrectomy is performed to prevent tumour seeding to the bladder. Earlier works warned about the risk of retroperitoneal metastasis and tumour spillage or port site recurrences[20,21]. EAU recommends that minimally-invasive techniques are contraindicated for invasive or large (T3/T4 and/or N+/M+) tumours given worse oncological outcomes[2]. Precautions suggested to lower the risk of tumour spillage include avoiding opening the urinary tract and avoiding direct contact between instruments and the tumour. In addition, avoiding morcellation of the tumour using an Endobag for tumour extraction and en bloc removal of the kidney and ureter with the bladder cuff is suggested to ensure the procedure is in carried out in a closed system[2].In modern practice however large tumours can still be managed in a minimally invasive fashion.

The first laparoscopic NU was described by Clayman et al. in 1991[22], prompting a new age of minimally-invasive techniques to be applied to the treatment of UTUC. The laparoscopic approach to the distal ureter and BCE can include a transvesical approach using a cystoscopic secured detachment and ligation method (CDL), or it can involve an extravesical approach using a laparoscopic stapling device with the stapling technique being associated with suboptimal oncologic outcomes[23].

Laparoscopic nephroureterectomy can be performed transperitoneally or retroperitoneally depending on surgeon preference, with retroperitoneal nephroureterectomy having the advantages of reducing bowel mobilization, reducing the risk of visceral injury and reducing the risk of ileus. In addition, if tumor spillage present, it would be confined to the extraperitoneal space[24]. The pure laparoscopic technique involves either extravesical stapling of the distal ureter or complete laparoscopic dissection of ureter and bladder cuff and suture closure of the bladder defect[25,26]. However, the pure laparoscopic technique is more difficult to perform and port site seeding has been reported[21]. The laparoscopic extravesical stapling approach has been associated with remnant ureteric orifice present post-excision in 50%

of the cases[27].

Robotic-assisted NU[28-30] is being increasingly utilised, with the aim of having equivalent oncological results to open surgery whilst limiting perioperative morbidity and minimising the technical challenges of laparoscopic surgery. It is less technically challenging than laparoscopic NU given the extra degrees of freedom and articulation of the robotic platform. Multiple reports[31-34] have been published documenting the perioperative feasibility and safety of the robotic approach as well as encouraging early oncologic outcomes. However, there is a dearth of long-term oncological outcomes following robotic-assisted NU. Early experience with this modality[35] as reported in 2008 involved patient repositioning and robot redocking throughout the procedure. However, innovations in this field have eliminated the need for this. Hemal et al.[34] was the first to describe a technique of robotic-assisted NU with BCE without requiring intraoperative patient repositioning or redocking of the robot. This technique allows for a seamless transition from upper tract to lower tract surgery without the need to reposition the patient or re-dock the robot. The three ports are strategically placed to allow access to the kidney, ureter, and bladder. After dividing the renal vascular structures, the ureter is clipped, though not divided. The ureter is then dissected distally as much as possible. In cases of ureteric tumours, wide dissection of the ureter is carried out to avoid a positive margin or entry into the ureter. Lymphadenectomy is also carried out. Bladder stay sutures are placed lateral to the ureterovesical junction to prevent retraction of the bladder once the bladder cuff is excised. It was reported that all fifteen patients were operated on successfully without perioperative complications, no positive surgical margins present and with no recurrences detected in the short-term.

Zargar et al.[32] describes a similar technique for robotic-assisted NU where there is also no need for patient repositioning or robot redocking. The approach to BCE involves dissecting the detrusor muscle until there is tenting of the bladder mucosa, followed by placement of lateral and medial 2-0 Vicryl polyglactin sutures. Following circumferential excision of the bladder cuff, the two sutures are tied together to close the bladder defect and ensure watertight closure. Another difference with this approach is port placement where the ports are all placed along the lateral rectus muscle to combine maximum accessibility for the nephrectomy portion of the surgery and further enabling pelvic access to facilitate proper bladder cuff dissection. There were no major complications in the thirty-one patients included in this series. NU using a three-arm robotic approach cannot only provide the surgeon with a more feasible approach for performing the operation, but also provides for a less expensive operation.

Comparing oncological and perioperative outcomes of endoscopic techniques with non-endoscopic techniques

17 studies were found that assessed oncological outcomes of endoscopic versus non-endoscopic techniques, as can be seen in **Table 1a**. The largest study found was a retrospective analysis of 2681 patients undergoing an open transvesical, open extravesical or endoscopic approach by Xylinas et al.[36], finding that the endoscopic approach was associated with higher rates of intravesical recurrence (34.1%) compared to the other two approaches (21.4% and 20.3%). As discussed previously, this lends credence to the issue of tumour spillage associated with the endoscopic approach. Interestingly, no differences in non-bladder recurrence and survival were seen between the approaches. Other large studies that compared endoscopic and non-endoscopic approaches such as Kapoor et al.[7] found that in 820 patients, open intravesical excision was associated with lower intravesical recurrence in comparison to endoscopic and extravesical approaches. On the other hand, Li et al.[40] analysed 301 patients and found that there was no statistically significant difference in recurrence-free and cancer-specific survival between endoscopic and non-endoscopic techniques. Allard et al.[48] found similar recurrence and metastasis rates in 110 patients who underwent either open or endoscopic approaches, with Lai et al.[46] also finding comparable intravesical recurrence rates, along with no statistically significant differences in cancer-specific and overall survival. Novel endoscopic approaches such as that described by Geavlete et al.[44] involving a variation of the pluck technique using bipolar plasma vaporisation found intravesical recurrences in 14% of patients.

8 studies were found that assessed perioperative outcomes of endoscopic versus non-endoscopic approaches as can be seen in Table 2a. Endoscopic approaches are generally associated with better perioperative outcomes, including shorter operating times, length of stay and less blood loss as can be seen in Table 3a. Fragkoulis et al.[38] collected data from 378 patients and found the endoscopic approach had a lower mean operating time of 115 minutes versus the open approach of 143 minutes. In another study, Gillan et al.[45] compared laparoscopic, endoscopic and open approaches, concluding that the endoscopic approach had the shortest mean operating time and estimated blood loss. Similarly, Pang et al.[51] found that operating time, length of stay and blood loss were lower in the endoscopic group compared with the open approach.

Comparing oncological and perioperative outcomes of open with minimally-invasive techniques

51 studies were found that assessed oncological outcomes of open versus minimally-invasive techniques, as can be seen in Table 1b. Ariane et al.[52] found a higher cancer-specific survival and reduced metastasis rate in those who underwent a laparoscopic versus an open approach. However, in an analysis of 159 patients Blackmur et al. did not find significant difference in 5-year survival between these two approaches. This was also seen with Fairey et al.[55], with no significant difference in overall survival seen between the two groups. Although Favaretto et al.[56] also found similar rates of cancer-specific and recurrence-free survival, there was a reduced number of intravesical recurrences seen in the laparoscopic (9.3%) versus the open group (31.5%). However, Walton et al.[59] found there to be no significant difference in non-bladder recurrence between the two groups. A meta-analysis by Piszczek et al.[97] also concluded that laparoscopic and open NU have comparable oncological outcomes, with no statistically significant difference present among any of the measured oncological outcomes (cancer-specific survival, overall survival, intravesical recurrence-free survival, recurrence-free survival).

Novel minimally-invasive techniques like the Agarwal PolyLoop Ligation Technique[19] has been shown to be oncologically valid in the long-term, with no cases of intravesical recurrence detected, and cancer-specific and overall survival comparable to other studies seen in the table.

Moschini et al.[98] compared oncological outcomes of laparoscopic versus open approaches using a propensity matching analysis approach, concluding that there is no difference in oncological efficacy (overall recurrence and cancer-specific mortality) between the two approaches. Another systematic review of open versus laparoscopic NU by Peyronnet et al.[99] concluded that there are worse cancer-specific survival and overall survival in patients who have locally advanced high-risk that have underwent laparoscopic NU compared to open NU. However, in another systematic review and meta-analysis between open and laparoscopic NU, Liu et al. (100) found that there was no significant difference in oncological and perioperative outcomes between the two techniques, but did note a longer mean operative time in those that underwent laparoscopic NU.

Nouralizadeh et al. (101) performed a meta-analysis comparing oncological and perioperative outcomes of open, laparoscopic, and hand-assisted laparoscopic NU, finding that the three techniques had comparable oncological outcomes, but with laparoscopic and hand-assisted laparoscopic NU having better perioperative outcomes when compared with open surgery. It was also found that a laparoscopic approach was associated with a longer operative time.

Looking at a perioperative standpoint as can be seen in Table 2b, minimally-invasive techniques are on average associated with a higher mean operating time but with less blood loss. As seen in table 3b, Ariane et al.[52], Favaretto et al.[56], Wang et al.[61], Greco et al.[64], Kitamura et al.[66] and Hanske et al.[94] report higher mean operating times versus open approaches. Favaretto et al.[56], Wang et al.[61], Simone et al.[63], Kitamura et al.[66], Waldert et al.[80] and Gillan et al.[45] found lower estimated blood loss with minimally-invasive approaches versus open procedures. Trudeau et al.[93] retrospectively analysed robotic-assisted NU vs laparoscopic NU and found that they perioperative complication rate for robotic-assisted NU was lower versus laparoscopic NU. In a systematic review by Mullen et al.[102] comparing open versus laparoscopic versus robotic-assisted NU, laparoscopic techniques were similarly found to be oncologically comparable to open NU but with improved perioperative outcomes (estimated blood loss and length of hospital stay). The paucity of high-quality evidence surrounding the use of robotic-assisted NU was noted and therefore no conclusions with respect to this modality could be drawn. However, estimated blood loss and hospital length of stay tend to be lower in the minimally-invasive groups versus the open approach. A similar 2019 systematic review and meta-analysis of over 87,000 patients by Veccia et al.[103] sought to compare robotic-assisted NU with other techniques (including open, laparoscopic and hand-assisted laparoscopic NU), also noting the lack of high quality data surrounding this topic and was unable to conclude the best technique for NU. They concluded that the techniques analysed in the review are all oncologically-valid, with more long-term oncologic data needed surrounding robotic-assisted NU.

Additional approaches to NU

Kidney-sparing surgery (KSS) is utilised for low-risk UTUC, as opposed to radical NU for high-risk disease. This is since radical NU significantly reduces the nephron mass by at least 50%, predisposing the patient to chronic kidney disease and associated increased risk of cardiovascular events, morbidity, and mortality. KSS has been shown to have comparable oncological outcomes compared to radical NU in low-risk disease [104,105], and as a result the European Association of Urology[2] recommends this modality for all low-risk patients irrespective of the status of the contralateral kidney, and in select patients with CKD or that have a solitary kidney[106]. Low-risk disease (localised, non-metastatic disease) is defined as having all of the following features: unifocal disease, tumor size less than 2 cm, low-grade cytology, low-grade URS biopsy and no invasive aspect on CT urography. An important point to note when offering KSS is that the patient must be willing to undergo repeated and stringent surveillance follow-up including upper tract imaging, flexible cystoscopy, ureteroscopy, and urine cytology[106].

CONCLUSIONS

Although endoscopic approaches have more favourable perioperative outcomes, this comes at the expense of increased risk of tumour spillage and recurrence compared to the traditional open approaches. Minimally-invasive techniques (laparoscopic and robotic-assisted NU) largely have superior perioperative outcomes versus their open NU counterparts, with comparable oncological outcomes. The majority of studies found were retrospective studies. Future directions should involve RCTs comparing minimally-invasive with open techniques. Ultimately the clinical characteristics of the patient, patient preference, access to novel technology and surgeon preference and expertise will continue to play a role in the approach to NU.

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